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A clinical trial on preventive effects of licorice on propranolol-related dizziness, a side-effect in patients with migraine headache

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Abstract

Background/Aims: This trial aimed to evaluate Licorice preventive effects on dizziness, a side effect of propranolol in patients with migraine headaches (systolic blood pressure <120 mmHg).

Methods: Forty patients (systolic blood pressure <120 mmHg) who received propranolol (prophylactic medicine) were subjected and divided into Licorice and placebo groups. Dizziness frequency and severity, systolic and diastolic blood pressure, and orthostatic hypotension were assessed after three months. Headache frequency and severity in groups were examined via the Migraine Disability Assessment Test (MIDAS) to evaluate the licorice impact on migraine and response to treatment.

Results: Dizziness frequency and incidence and orthostatic hypotension incidence were significantly reduced in the Licorice group more than those of placebo, while dizziness severity was almost similar. Finally, systolic and diastolic blood pressure values increased in the Licorice group and decreased in the placebo. MIDAS and headache severity in both groups were the same. However, headache frequency in the Licorice group was lower than the placebo.

Conclusion: Licorice maybe effective for the prevention of propranolol-induced dizziness and hypotension in patients with migraine headaches (systolic blood pressure <120 mmHg). Furthermore, licorice may increase patient tolerance in receiving propranolol and ameliorate migraine attack frequency.

Keywords: Migraine; Dizziness; Orthostatic hypotension; Licorice; Propranolol.

Introduction

Headache disorders are of the most common health problems throughout the world [1]. It is a worldwide problem, affecting many people in different geographical areas of all ages and races. It has been estimated that 50% of adults have experienced at least one headache within the last year. About three-quarters of adults aged 18-65 years have been reported with migraine headaches [2]. The prevalence of this disorder is higher in women than men [3].

Headaches are caused by tension, displacement, inflammation, vascular spasm, or swelling of pain-sensitive structures in the head or neck [4]. This disorder is divided into two categories: Primary which includes Tension-Type Headache (TTH) and migraine; secondary headache disorders. The migraine itself classified as migraine without aura and migraine with aura [5,6].

According to European studies, Migraine is a primary headache with a genetic basis that affects 6-8% of men and 15-18% of women aged 35-45 years old, for each year. However, children can also suffer from migraines [7].

Pathophysiologically, the release of inflammatory substances around the nerves and blood vessels of the head may cause pain. Migraine headache is commonly one-sided and/or pulsating and lasts for hours to 2-3 days. This disorder can accompany with nausea and sometimes vomiting and/or dislike or intolerance of normal levels of light and sound. In addition to being painful, migraines can also be debilitating and may affect the quality of life, social activity, and employment. Therefore, prevention of the headache and the appropriate treatment with minimal side effects is important [2].

Pharmacological management lines for migraines are commonly analgesics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and tryptamine-based medicines. Preventative migraine medications aim to lessen the frequency of migraine attacks and unwanted effects. Many classes of medicaments such as beta-blockers, anticonvulsants, calcium channel blockers, and tricyclic antidepressants are currently administered for the prevention of migraine attacks [8].

Beta-blockers may affect the central catecholaminergic system and brain serotonin receptors but the exact mechanism of them is unclear.

Propranolol is a beta-blocker that is commonly used for migraine prophylaxis. However, a wide range of side effects like bradycardia, hypotension, bronchospasm, gastrointestinal complaints, and vertigo may limit some patients to use [9].

The suggested dose for migraine prevention with propranolol is in two divided doses, starting at 40 mg daily; dose ranged from 40 to 160 mg daily [10]. However, patients usually do not tolerate high doses of this medication. Low tolerance and mentioned adverse effects might be of usual causes of migraine treatment failure. Hypotension and dizziness are the most adverse effects reported in nearly 10% of patients. Different approaches and medications have been used to manage the dizziness of propranolol [11,12].

Efforts to discover new drugs, especially from herbal medicines are considered by clinicians and researchers. Licorice (Glycyrrhiza glabra L. from the family, Fabaceae) is a plant used traditionally for the management of gastrointestinal, respiratory, and blood circulation systems [13].

Glycyrrhetinic acid and glycyrrhetic acid are active parts of licorice that inhibit 11-beta hydroxyl-steroid dehydrogenase in kidney and peripheral metabolism of cortisol [13,14]. Licorice also inhibits NADPH dependent short-chain dehydrogenase reductase in the kidney resulting in the elevation of blood pressure [15]. The impact of Licorice on blood pressure has also been evaluated in patients with diabetes, polycystic ovarian syndrome, and Addison's disease [16-18].

Concerning these related studies, current work aimed to evaluate the effect of licorice on increasing the tolerance and ultimately better response to treatment in patients who have used propranolol as a prophetic agent for migraines.

Methods

Study design

This study was a double-blind randomized clinical trial with two arms defining as the Licorice group and Placebo. The protocol was approved by the ethics committee at Shiraz University of Medical Sciences, registered at Iranian Registry of Clinical Trials (IRCT2014092219253N1), and carried out at two related polyclinics at the south of Iran (Emam Reza and Shahid Motahari polyclinics, related to Shiraz University of Medical Sciences) from June 2018 to October 2019.

Participants

Forty Patients with migraines according to IHS (International Headache Society) were enrolled in this study. Patients were informed about the study and details of the protocol by the clinician at Emam Reza and Shahid Motahari polyclinics. The sample size for this trial was determined based on previous related [18]. Patients were randomly allocated to two equal groups as Licorice and Placebo. Simple randomization was considered for this trial. Patients were randomly divided into two groups as placebo and Licorice. Based on simple randomization, forty rigid numbers from 1 to 40 were written on 40 pieces of paper. These papers were mixed and then randomly 20 pieces of those were picked and considered as the Licorice group. The remaining numbers were also considered as a placebo group. There were 20 patients in each group, all of them signed consent forms and declared their satisfaction to participate. The patients were adults above 18 years old with migraine headaches and systolic blood pressure <120 mmHg.

Patients who had evidence of hypertension, renal failure, liver disease, adrenal disorders such as Addison's syndrome, and pregnant women as well as those with hypersensitivity to Licorice were excluded from the study. To check these criteria, para-clinic tests were carried out for patients. Blood pressure was examined for each participant prior enrolling to the study. On the other hand, patients were asked to inform the physician if they might have hypersensitivity to natural medicines or raw medicinal plants.

Preparation of Licorice capsules

Freeze-dried aqueous extract of Glycyrrhiza glabra L. root powder was purchased from Shirin Darou (www.shirindarouco.

com) Company, Shiraz, Iran. Employed capsules were filled up to 350 ± 5 mg (yielded from 1400 ± 20 mg of root dry crude powder). Capsuled were all filled at the Preparation center for Traditional Persian Pharmacy, an isolated clean laboratory site at Shahid Motahari polyclinic. Placebo capsules were filled with roasted starch and 10% w/w of root dry crude powder up to overall 350 ± 5 mg. All capsules were in the same green color and additionally capsuled were packed in uniform containers.

Interventions

Patients in Licorice group took 20 mg propranolol two times a day, 250 mg Sodium Valproate once a day in addition to 6 Licorice capsules for first 2 months and subsequently, they took 40 mg propranolol two times a day, 250 mg Sodium Valproate once a day and 6 Licorice capsules for the third month.

In parallel, placebo group took 20 mg propranolol two times a day, 250 mg Sodium Valproate once a day in addition to 6 placebo capsules for first 2 months and subsequently, they took 40 mg propranolol two times a day, 250 mg Sodium Valproate once a day and 6 placebo capsules for the third month. Patient adherence to the drug regimen was assessed via the pill count method. The patients received their medications every month and the number of used and remaining unused capsules was recorded. Also, any adverse events were recorded during each visit. The general condition of each patient was monitored every 2 weeks and probable adverse events were recorded via a phone call.

Outcomes

At the end of the protocol (third month), blood pressure was measured in supine and standing position, and MIDAS (Migraine Disability Assessment) and dizziness questionnaires were collected. These parameters were also examined at the starting point as the baseline. In this study, frequency of headache, headache severity, systolic and diastolic blood pressure, weight, incidence, severity, and frequency of dizziness caused by propranolol were assessed.

Statistical analysis

Statistical analyses were performed by SPSS version 18. Categorical or descriptive data was shown as percent and quantitative data was presented as Mean ± SD. Datanormality was evaluated with the Kolmogorov Simonov test. Normal parameters were evaluated by the t-test and Mann-Whitney was used as a nonparametric test. This was performed to evaluate the primary outcomes between the two groups. To validate the data and controlling the baseline, ANCOVA analysis was also considered.

Results

Forty migraine patients fulfilled the protocol. Thirty-one patients (77.5%) were female and 9 (22.5%) were male who was also the same in Licorice and placebo groups. Tomigraine distribution between the sexes in society. Table 1 represented the demographic information for all patients in both groups. Thirty-six patients completed the trial. Two patients in the Licorice group dropped out because of lip dryness andout of interest, two in the placebo group dropped out according to dizziness and migration to another city (Figure 1).

Patients in Licorice and placebo groups at baseline regarding demographic parameters had no significant differences.

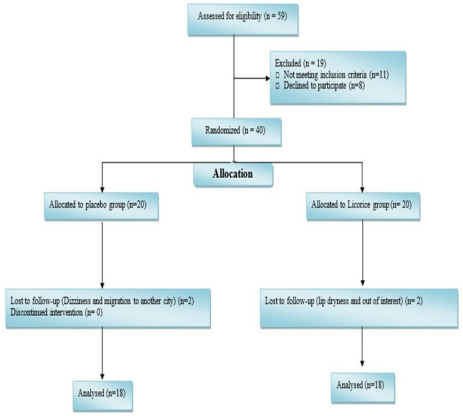

Figure 1: The diagram of patients enrolment.

The effect of either Licorice or placebo on the frequency of headache, headache severity, systolic and diastolic blood pressure, weight, incidence, severity, and frequency of dizziness caused by propranolol were assessed at baseline and the end of the protocol. According to Table 1, there were no differences between the mentioned parameters for both groups at the baseline. On the contrary, the Licorice group showed statistically significant differences concerning headache frequency, systolic and diastolic pressures, and frequency of dizziness, as compared to those of the placebo group (Table 1,2). On the other hand, in the Licorice group, frequency and severity of headache, systolic and diastolic blood pressure, and frequency of dizziness were significantly different at the end of the protocol, as compared to the respective baseline. However, the Licorice group did not represent differences in severity of dizziness (Table 1,2). Moreover, there was no statistically significant weight gain at the end of the study in this group. On the other side, differences in weight gain and systolic blood pressure were not significant in the placebo group at the end of the study (Table 1,2).

Categorical or descriptive data including orthostatic hypotension and incidence of dizziness were also assessed in this study. Accordingly, the Licorice group showed better outcomes regarding these parameters at the end of the study, as compared to the placebo. It is considered that there were no differences between the two groups at the beginning of this assessment (Table 3,4).

Although there were promising outcomes in the Licorice group for improvement of the studied parameters, however, no significant difference was observed regarding MIDAS grade between Licorice and placebo groups.

During the study, no serious side effects have been reported by patients in both groups. Therefore, adding licorice to the regimen of migraine headache prevention does not reduce the therapeutic effects of propranolol in preventing migraine and Licorice does not worsen the headache.

During the study, no serious side effects have been reported by patients in both groups.

Table 1: Demographic and clinical characteristics related to the effectiveness of Licorice and placebo before and after 3 months (final).

Variable	Groups	Mean ± SD (Baseline)	Mean ± SD (Final)	*p*-value of intra-group comparison
Sex	Licorice (Female)	80%		
	Licorice (Male)	20%		
	Placebo (Female)	75%		
	Placebo (Male)	25%		
	p-value of between-group comparisons	0.678		
Age	Licorice	33.15 ± 6.89		
	Placebo	31.78 ± 7.11		
	p-value of between-group comparisons	0.745		
Frequency of headache	Licorice	24.25 ± 10.42	5.95 ± 2.43	0.000
	placebo	23.45 ± 11.32	12.05 ± 7.85	0.003
	p-value of between-group comparisons	0.899	0.028	
Systolic blood pressure	Licorice	102.75 ± 7.85	115 ± 8.27	0.000
	placebo	105.22 ± 9.40	98.75 ± 10.24	0.017
	p-value of between-group comparisons	0.165	0.000	
Diastolic blood pressure	Licorice	62.5 ± 9.66	74.25 ± 12.06	0.000
	placebo	60.5 ± 10.50	58 ± 11.51	0.30
	p-value of between-group comparisons	0.53	0.000	
Headache severity	Licorice	7.00 ± 1.62	4.48 ± 2.55	0.01
	placebo	7.05 ± 1.66	5.14 ± 1.64	0.01
	p-value of between-group comparisons	0.92	0.42	
Effect on weight	Licorice	65.90 ± 11.04	66.90 ± 11.03	0.17
	placebo	62.60 ± 10.80	62 ± 10.02	0.28
	p-value of between-group comparisons	0.34	0.15	
Frequency of dizziness caused by Propranolol	Licorice	9.40 ± 3.21	1.10 ± 0.57	0.001
	placebo	5.30 ± 2.77	15.30 ± 2.21	0.006
	p-value of between-group comparisons	0.28	0.01	
Severity of dizziness caused by Propranolol	Licorice	1.35 ± 0.46	0.50 ± 0.28	0.07
	placebo	0.70 ± 0.37	1.60 ± 0.53	0.01
	p-value of between-group comparisons	0.14	0.07	

Table 2: Intra-group outcomes related to the effectiveness of Licorice and placebo before and after 3 months (final).

Variable	Groups	Mean ± SD (Baseline)	Mean ± SD (Final)	*p*-value
Frequency of headache	Licorice	24.25 ± 10.42	5.95 ± 2.43	0.000
	placebo	23.45 ± 11.32	12.05 ± 7.85	0.003
Systolic blood pressure	Licorice	102.75 ± 7.85	115 ± 8.27	0.000
	placebo	105.22 ± 9.40	98.75 ± 10.24	0.017
Diastolic blood pressure	Licorice	62.5 ± 9.66	74.25 ± 12.06	0.000
	placebo	60.5 ± 10.50	58 ± 11.51	0.30
Headache severity	Licorice	7.00 ± 1.62	4.48 ± 2.55	0.01
	placebo	7.05 ± 1.66	5.14 ± 1.64	0.01
Effect on weight	Licorice	65.90 ± 11.04	66.90 ± 11.03	0.17
	placebo	62.60 ± 10.80	62 ± 10.02	0.28
Frequency of dizziness caused by Propranolol	Licorice	9.40 ± 3.21	1.10 ± 0.57	0.001
	placebo	5.30 ± 2.77	15.30 ± 2.21	0.006
The severity of dizziness caused by Propranolol	Licorice	1.35 ± 0.46	0.50 ± 0.28	0.07
	placebo	0.70 ± 0.37	1.60 ± 0.53	0.01

Table 3: Effect of licorice on orthostatic hypotension at baseline and after 3 months (final).

Groups	Time	Patients with Orthostatic Hypotension (%)	Patients without Orthostatic Hypotension (%)	p-value
Licorice	At baseline	15%	85%	0.292
Placebo		5%	95%	
Licorice	Final point	0%	100%	0.002
Placebo		40%	60%	

Table 4: Effect of licorice on the incidence of dizziness at baseline and after 3 months (final).

Groups	Time	Patients with dizziness (%)	Patients without dizziness (%)	*p*-value
Licorice	At baseline	60%	40%	0.113
Placebo		35%	65%	
Licorice	At the	25%	75%	0.004
Placebo		70%	30%	

Discussion

Orthostatic hypotension is a phenomenon that occurs with upright posture as a result of marked blood pressure reduction which can cause dizziness, syncope, and even angina or stroke. In different reports, orthostatic hypotension prevalence varies from 5 to 20 percent. Orthostatic hypotension occurs as a result of many disorders or drug side effects [19].

Many medications such as Terazosin, Trazodone, Levodopa, Pramipexole, Ropinirole, Olanzapine, Risperidone, Propranolol, Hydrochlorothiazide, Furosemide, Tizanidine, Morphine, Sildenafil, Tadalafil, Temazepam, Hydralazine, and Nitroglycerin can cause orthostatic hypotension [20].

On the other hand, different Pharmacologic and non-pharmacologic therapy were used to reduce symptoms of orthostatic hypotension although limited evidence supports the sufficiency of these therapies [21,22]. As a fact, herbal substances have been employed to manage and cure various types of disorders. Licorice is one of the most famous and important medicinal herbs that have been repeatedly mentioned as a cure for headaches and related complications [23].

Although no significant differences were identified on orthostatic hypotension between two groups at baseline (p=0.292), after the treatment protective effect of Licorice on orthostatic hypotension was observed (p=0.02).

The purpose of this study was to evaluate the preventive effects of licorice on dizziness as a side effect of propranolol in 40 patients with migraine headaches (systolic blood pressure < 120 mmHg).

In both groups, significant changes were observed after the treatment concerning baseline in systolic blood pressure. Systolic blood pressure was increased in the Licorice group (P<0.001) and decreased in the placebo group (P=0.017); also significant differences in systolic and diastolic blood pressure were observed between two groups at the end of the study (P<0.001).

So Licorice with its mineralocorticoid effect prevent the hypotension in the Licorice group and receiving propranolol alone led to a decrease in blood pressure in the placebo group. This phenomenon was reported by study the effect of Licorice in hypotension related adverse effect in the use of diuretics [16] (Both indicated an increase in blood pressure).

Decreasing blood pressure in the placebo group, which had pre-existing systolic pressures <120, result in dizziness or a significant increase in the frequency of dizziness during treatment. As a result, Licorice has protective effects on the frequency of dizziness caused by Propranolol and could be considered as an effective ingredient in the prevention of dizziness caused by propranolol.

However, the protective effect of licorice on the severity of dizziness was not proved.

In the Licorice group, after the intervention, no evidence of orthostatic hypotension was observed. On the other hand, orthostatic hypotension was observed in the placebo group as an adverse effect of propranolol. Therefore Licorice has protective effectson orthostatic hypotension induced by Propranolol.

This result can be justified by the mineralocorticoid effect of Licorice due to inhibiting the enzyme 11-beta hydroxysteroid dehydrogenase enzyme in the kidney, which increases the cortisol concentration, water retention and, consequently, increased blood pressure. This result was similar to Murakami's study.

In both groups, significant changes were observed after the treatment about baseline in frequency of headache. However, the frequency of headaches was significantly lower in the placebo group. So Licorice by increasing patients' tolerance results in better response to treatment. Weight gain and electrolyte imbalance (especially hypokalemia) were assessed as side effects of Licorice. Because the decrease in potassium level usually occurs after 6 weeks, serum potassium was measured in patients after 6 weeks. None of the 40 patients had any electrolyte disturbances.

Licorice increased the weight of patients in the Licorice group by an average of 1 kg, however, it was not significant (p=0.17). The placebo group did not have any specific weight change.

Taken as a whole, the application of Licorice with propranolol may reduce the incidence of dizziness and hypotension in patients with systolic blood pressure < 120 mmHg. As a result, by increasing the patients' tolerance using Licorice in association with commonly related medicaments, it leads to better response to treatment, while the use of licorice is not in conflict with migraine headaches.

This work has also some limitations. First of all, a small number of patients, second relatively short period of follow-up, and limited parameters for comprehensive evaluation. Accordingly, further investigation is necessary to validate the results of this current clinical trial.

Conclusion

The results of this study indicate the efficacy of Licorice in the prevention off frequency of dizziness caused by Propranolol. Moreover, Licorice with its mineralocorticoid effect showed protective effects on orthostatic hypotension occurrence. Also, it is recommended that clinical trials with a larger sample size are necessary for evaluation of Licorice utilization safety in different populations who consume propranolol for migraine prophylaxis.

Declarations

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Author contributions: Conceptualization: PP. Methodology: PP and MMZ. Investigation: ZB, Formal analysis: ZB and PP. Writing – original draft: MMZ, SA. Writing – review & editing: MMZ and PP. Supervision: MMZ and PP.

Conflict of interest: The authors of this manuscript declare that they have no conflict of interest.

Ethical statement: This research was approved by the ethics committee at Shiraz University of Medical Sciences (CT-P-9347-4147).

Data availability: The used and analyzed datasets during the current study are available from the corresponding author upon any reasonable request.

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